REMARKS

Applicants request reconsideration of the above-identified application in view of the foregoing amendments and following remarks.

Applicants have amended the Title to more specifically indicate the currently claimed invention.

Applicants have cancelled claims 2 and 25, as redundant in view of the amendments to claims 1 and 24 from which claims 2 and 25 formerly depended. Applicants have amended claims 1 and 24 to recite a mouse rather than a non-human mammal and a promoter which directs central nervous system or neuronal expression of the APP695 transgene. Support for amended claims 1 and 24 can be found on page 11, lines 3-7 of the specification. They have amended claim 3 to make it dependant from claim 1, instead of on cancelled claim 2. Applicants have amended claims 1, 3 and 24 in reply to the Examiner's rejections as detailed below. Applicants have added new claims 36 and 37. Support for new claims 36 and 37 can be found on page 11, lines 3-7 of the specification. Applicants have amended withdrawn claims 8-10 and 29. Support for amended claims 8-10 can be found on page 4, line 20 to page 6, line 9 of the specification. Support for amended

claim 29 can be found in Figure 3 and Example 4 in the specification.

Therefore, claims 1, 3-7, 24, 26-28 and 36-37 are now pending in this application.

None of the proposed amendments or added claims is new matter.

The Objection

Specification (Title)

The Examiner contends that the title of the invention is not descriptive and states that a new title is required clearly indicating the invention to which the claims are directed. Without acquiescing to the Examiner's contention, applicants have amended the title to "Transgenic Mouse Model of Neurodegenerative Disorders," thus obviating the Examiner's objection.

The Rejections

35 U.S.C. § 112, First Paragraph: Written Description

The Examiner, pointing to and construing various documents, has rejected claims 1-7, 24-25, 27 and 28 under 35 U.S.C. § 112, first paragraph, because allegedly the specification, "while enabling for transgenic mice which contain and [express] an APP_{695} transgene in their brains comprising an amino acid substitution at amino acids 670, 671 and 717 operatively linked to a neuronal promoter, where the expression of the transgene produces abnormal Aβ deposition in the central nervous system of said mouse's brain, does not reasonably provide enablement for transgenic non-human mammals

and the use of any type of promoter." The Examiner, thus, contends that the specification does not enable any person skilled in the art to make or use the invention commensurate with these claims. Applicants traverse.

As noted by the Examiner, the specification is enabling "for transgenic mice which contain and [express] an APP695 transgene in their brains comprising an amino acid substitution at amino acids 670, 671 and 717 operatively linked to a neuronal promoter..." While applicants disagree with the Examiner's assertion that only mice are enabled, solely to expedite prosecution, applicants have amended claims 1 and 24 to recite a "transgenic mouse" and claim 29 to recite "mouse." This overcomes part of the rejection.

Applicants also traverse the Examiner's attempt to restrict the claims to a specific promoter. However, solely to expedite prosecution, applicants have amended claims 1 and 24 to recite a promoter which "directs central nervous system or neuronal expression of said transgene." Exemplary central nervous system and neuronal promoters, such as the neuron specific enolase gene promoter, the human platelet derived growth factor B subunit promoter, the Thy-1 promoter and the neurofilament promoter are disclosed in the specification (see page 11, lines 3-7). The specification also teaches that the

cosTet prion promoter directs position-independent transgene expression in the CNS (see for e.g. page 10, line 24 to page 11, line 2 of the specification and Examples 1 and 3).

In addition, applicants have added claims 36 and 37 drawn to specific promoters which direct central nervous system (CNS) or neuronal expression of the APP695 transgene.

Applicants respectfully request that the Examiner withdraw this rejection.

35 U.S.C. § 103(a): Obviousness

The Examiner has rejected claims 1-2, 4, 6-7, 24-25 and 27-28 as allegedly being unpatentable over United States patent 6,509,515 ("Hsiao"). The Examiner states that "the claims broadly encompass the use of any promoter and [that] no specific phenotype is recited to occur in the resulting transgenic animal." The Examiner asserts that Hsiao teaches that all three APP_{695} mutations were known in the prior art, contemplated for use in generating transgenes for use in transgenic models and that while there is no specific teaching or reduction to practice by Hsiao, that Hsiao provides the teachings necessary to generate the claimed transgenic animal. The Examiner also states that the specific combination of the

three APP_{695} mutations were reduced to practice in the prior art with a different form of APP.

The Examiner additionally contends that "[without] reduction to practice and the general unpredictability of the art of transgenics, the specific outcome/phenotype can not be predicted precisely, however in the view of the art of Alzheimer's as a whole, there would be a general expectation that greater amounts of alterations associated with the disease would result in a more dramatic phenotype. Moreover, the unexpected phenotype is demonstrated when expression is affected by one promoter and only in the mouse." Thus, the Examiner contends that the unexpected results would not extend to the use of any promoter in any non-human mammal. Applicants traverse.

The claimed transgenic animals display an unexpected improvement over those in the prior art. Specifically, page 22, lines 18-20 of the specification and Example 1 teach that the claimed transgenic animals display visible plaque deposits as early as 60 days after birth with robust plaques being visible at 90 days. Such a timeframe for plaque development is a marked improvement over the models of the alleged prior art which may not develop evidence of plaques until 6-9 months of age. Table 1 in the specification also shows that, in the

comparative experiment described in that table, the claimed TgCRND8 mouse (last line of Table 1 and Example 1) displays a desirable phenotype in a much shorter timeframe than the Tg2576 mouse (second line of Table 1). This Tg2576 mouse is the same mouse as that disclosed in Hsiao (Example 8 in column 37 of Hsiao).

According to the Examiner, the cited documents recite that a plurality of APP isoforms exist and that several mutations, taken either singly or in combination with each other, can been attributed to varying levels of Aβ plaque deposition. However, as stated by the Examiner, the general unpredictability of the art of transgenics does not allow one to predict the specific outcome that would occur as a result of the expression of one APP isoform with a specific set of mutations.

The Examiner also argues that Hsiao teaches that all three APP695 mutations (at positions 670, 671 and 717) were known in the prior art and that Hsiao provides the teachings necessary to generate the claimed transgenic animal. Hsiao, however, states that while it can be used, "it is unnecessary to use a coding sequence derived from an APP Gene with a mutation at the 717 locus" (see column 12, lines 34-40 of the specification). Thus, Hsiao teaches away from the claimed

invention and there is nothing in Hsiao, or anywhere else, to guide one skilled in the art to the conclusion that of the many possible combinations of APP transgene lengths and mutations, that the use of the APP695 transgene with mutations at positions 670, 671 and 717 would lead to the transgenic mice having the unexpected and improved properties that characterize the mice of the instant invention.

Thus, applicants respectfully request that the Examiner withdraw this rejection.

CONCLUSION

Applicants request that the Examiner reconsider and withdraw all outstanding objections and rejections, enter the amendments, and pass the resulting claims to allowance.

Respectfully submitted,

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